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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,786	11/08/2000	Sudhir Agrawal	47508.700	2469

23483 7590 06/19/2002

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 06/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/708,786	Applicant(s) AGRAWAL, SUDHIR	
	Examiner Terra Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-27 are pending in the instant application.

Oath/Declaration

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Applicant's Residence and Citizenship have been altered. No initials or dates have been made to verify changes. Appropriate correction is required.

Election/Restrictions

Applicant's election with traverse of oligonucleotide phosphorothioates and phosphorodithioates in Paper No. 8 filed 2/7/02 is acknowledged. The traversal is on the ground(s) that one species of polyanion will reveal art to other species of polyanion. This is not found persuasive because search for an oligonucleotide would not find "heparin" or "dextran sulfate", for example.

The requirement is still deemed proper and is therefore made FINAL.

Specification

Claim 1 is objected to because of the following informalities: On page 8 and 12, Oligo 1 is specified as a compliment to the mdm-2 oncogene. However, on page 14, paragraphs 2 and 3, Oligo 1 is specified as being compliment to the mdm-1 oncogene. Appropriate correction is required.

Nucleotide and/or Amino Acid Sequence Disclosure

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 1.821 through 1.825 for the reason(s) set forth below. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 Fed. Reg. 18230, May 1, 1990. It is noted that the application fails to comply with 37 CFR 1.821(d).

37 CFR 1.821(d) states, "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application".

Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

Claim Objections

Claim19 is objected to because of the following informalities: Claim 19 contains an inappropriate comma (see line 3). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "a method for statistically significantly potentiating the activity of a prodrug without producing significant side effects, the method comprising co-administering a polyanion (oligonucleotide phosphorothioate and phosphorodithioate) with the prodrug, wherein the polyanion (oligonucleotide phosphorothioate and phosphorodithioate) is not an oligonucleotide having two 5' and four 3'2'-O-methylribonucleosides and having the sequence 5' UGACACCTGTTCTCACUCAC-3'." It is unclear whether Claim 1 is *including* or *excluding* said sequence.

Claims 1, 10 and 19 (see claim 1 lines 1-3, claim 10 lines 1-3 and claim 19 lines 1-3) recite, "a method for statistically significantly potentiating the activity of a prodrug without producing significant side effects, the method comprising co-administering a polyanion (oligonucleotide phosphorothioate and phosphorodithioate) with the prodrug". It is unclear what is meant by statistically significantly potentiating the activity of a prodrug without producing significant side effects. Without a specific definition of what is "statistically significant", one of ordinary skill in the art is not apprised of the metes and bounds of the claim. (For example, by what statistical meter would such values be determined and what values would be deemed significant?). Additionally, without a specific definition of what are "significant side effects", one of ordinary skill in the art is not apprised of the metes and bounds of the claim. (For example, what side effect would be considered significant?). Clarification is required.

Claims 2-9, 11-18 and 20-27 are rejected as they depend from claims 1, 10 and 19.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-18 and 19-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for potentiating the activity of Campostar (CPT-11) efficacy by an oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 and an oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with the sequence of Oligo 2 by i.p. administration, does not reasonably provide enablement for statistically significantly potentiating the activity of a prodrug without producing significant side effects, the method comprising co-administering a polyanion (oligonucleotide phosphorothioates or phosphorodithioates) with the prodrug. The specification does not enable any person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without performing undue trail and error experimentation to practice the current invention.

The invention is broadly drawn to a method comprising co-administration of a prodrug with a polyanion (oligonucleotide phosphorothioates or phosphorodithioates) in a manner that potentiates the activity of the prodrug without producing significant side effects.

Ikuno et al. (J Natl Cancer Inst. 1995 December 87:1876-1883) assert, A major toxic effect of prodrug CPT-11 is severe diarrhea (see first paragraph). Ikuno et al. disclose, CPT-11 may produce characteristic mucosal changes in the intestine by inducing apoptosis and cell differentiation and further assert that the observed changes are likely to cause mal-absorption of water and electrolytes and hyper-secretion of mucin.

Sadzuka et al. (Jpn J Cancer Res 1997 May;88(5):512-6) disclose the effect of CPT-11 on lipid peroxide level in mouse tissues. Sadzuka et al. assert, "After CPT-11 (100 mg/kg, i.p.) administration, the lipid peroxide level in the heart increased 1.5 fold (mice) and 1.3 fold (rats) over the control levels" (see Abstract). Sadzuka et al. further disclose that CPT-11 may cause cardio-toxicity and pulmotoxicity and suggest that in both single and combination treatment with CPT-11, the possibility of side effects should be taken into consideration.

Cersosimo (The Annals of Pharmacotherapy 1998 December;32:1324-1332) disclose, "The dose-limiting adverse effects associated with irinotecan (CPT-11) are myelosuppression and diarrhea".

Ratain et al. [W.O. Patent No. 96/01127] disclose, "both diarrhea and myelosuppression have been significant concerns, with severe and/or life threatening toxicity being common" (see page 3 lines 13-15).

The instant invention specification provides general methodologies for survival times for mice with and without Camptosar (CPT-11) treatment and/or co-administration with modifications of Oligo 1 and Oligo 2.

The specification as filed shows that treatment of Campostar (CPT-11) and co-administration with modified phosphorodithioate oligonucleotides, Oligo 1 and Oligo 2, does not

adversely affect the survival times of such treated mice. These examples do not demonstrate that the deleterious effects observed in the prior art above were avoided upon co-administration of CPT-11 with modified phosphorodithioate oligonucleotides, Oligo 1 or Oligo 2. For example, the specification is silent on diarrhea, mucosal changes in the intestine, myelosuppresion or lipid peroxide levels. The specification as filed does not show any specific link of CPT-11 and oligonucleotide administration to any specific side effect such that treatment with CPT-11 and an oligonucleotide would be an apparent treatment option, for example. The prior art assert that despite the evidence in support of a role CPT-11 in anti-cancer therapies, CPT-11 is associated with various side effects including, but not limited to diarrhea, nausea and vomiting, stomatitis, alopecia, and asthenia (Cersosimo, 1998). This assertion appears to indicate that much work needs to be done to elucidate the side effects of CPT-11 such that one of ordinary skill in the art would know how to target CPT-11 and combination therapies thereto without producing significant side effects.

The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trial and error experimentation. The specification does not provide a meaningful nexus between co-administration of a prodrug with phosphorothioate oligonucleotides without producing significant side effects. It is unpredictable as to whether co-administration of a prodrug with phosphorothioate oligonucleotides will target any specific side effect. Phosphorothioate oligonucleotides are greatly desirable biological agents for reasons well known in the art. However, it is also well-known in the art that the design of phosphorothioate oligonucleotides as therapeutic agents is unpredictable because the biological effects could be non-specific in nature.

Furthermore, it is unpredictable that any unspecified, undisclosed, undescribed phosphorothioate oligonucleotide co-administered with a prodrug would not produce significant side effects.

One of skill in the art would have to engage in trial and error experimentation to develop methods of co-administering a prodrug with a phosphorothioate oligonucleotide without producing significant side effects. In view of the unpredictability of the art, the quantity of experimentation required would include the specific quantity of the prodrug and the phosphorothioate oligonucleotide that result in the potentiation of the prodrug without producing significant side effects. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (Int J Oncol 1999, Oct;15:653-60).

Claims 1, 10 and 19 are drawn to a method for potentiating the activity of a prodrug without producing significant side effects, the method comprising co-administering a polyanion (phosphorothioate oligonucleotide) with the prodrug.

Wang et al. disclose that phosphorothioate oligonucleotides co-administered with DNA damaging agents, HCPT and adriamycin, synergistically inhibit tumor growth in nude mice (see page 653, Abstract).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Totora et al., (Proceedings of the National Academy of Sciences, 1997, 94:12586-91), Wang et al., Chen et al. [U.S. Patent 6013786] and Baracchini et al. [U.S. Patent No. 5,801,154].

Claims 1-27 are broadly drawn to a method comprising co-administration of a prodrug with a polyanion (oligonucleotide phosphorothioates or phosphorodithioates) in a manner that potentiates the activity of the prodrug without producing significant side effects.

Tortora et al. have taught synergistic inhibition of human cancer cell growth by cytotoxic drugs and a phosphorothioate antisense oligonucleotide. Tortora et al. further teach a method to study whether any cooperative effect may occur between the phosphorothioate antisense oligonucleotide and a series of cytotoxic drugs acting by different mechanisms (see page 12591 last paragraph).

Wang et al. have taught an mdm-2 oncogene as a novel target for human cancer therapy using a polyanion (oligonucleotide phosphorothioate) approach. Wang et al. further teach that

following administration of an anti-MDM2 phosphorothioate antisense oligonucleotide, *in vivo* antitumor activity was observed in nude mice. Moreover, *in vivo* synergistically therapeutic effects of MDM2 inhibition and DNA damaging agents, adriamycin and 10-hydroxycamptothecin (HCPT) were observed (see Abstract). Wang et al. assert the future development of anti-MDM2 antisense oligonucleotide phosphorothioate as a cancer therapeutic agent used alone or in combination with conventional chemotherapeutics.

Chen et al. have taught the potential synergistic effects between mdm-2 antisense phosphorothioate oligonucleotide inhibition and DNA damage inducing agent, HCPT. Chen et al. have further taught oligonucleotide and HCPT co-administration and its effects on anti-tumor activities.

Totora et al, Wang et al. and Chen et al. have not taught phosphorothioate oligonucleotides with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions and oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions.

Baracchini et al. have taught phosphorothioate oligonucleotides with 2'-O-methylribonucleoside modifications at varying positions. Baracchini et al. have further taught, "In the context of this invention, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid or deoxyribonucleic acid. This term includes oligonucleotides composed of naturally-occurring nucleobases, sugars, and covalent intersugar (backbone) linkages as well as oligonucleotides having non-naturally-occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic

acid target and increased stability in the presence of nucleases. Specific example of some preferred oligonucleotides envisioned for this invention include those containing modified backbones, for example, phosphorothioates" (see Column 6 lines 18-38). Baracchini et al. further teach designed phosphorothioate oligonucleotides with 2-O-methyl modifications (see Table I). Baracchini et al. assert that phosphorothioate oligonucleotides with 2-O-methyl modifications are particularly useful for oral administration (see column 4, lines 48-49).

In view of Totora et al, Wang et al., Chen et al. and Baracchini et al., it would have been obvious to one of ordinary skill in the art to co-administer a prodrug with a phosphorothioate oligonucleotide in a manner that potentiates the activity of the prodrug without producing significant side effects. One of ordinary skill in the art would have been motivated to potentiate the activity of a cytotoxic prodrug, such as CPT-11, with phosphorothioate oligonucleotides since Tortora et al. teach synergistic inhibition of human cancer cell growth by cytotoxic drugs and phosphorothioate antisense oligonucleotides. One of ordinary skill in the art would have been motivated to co-administer CPT-11 with Oligo 1 (mdm-2 oncogene) in a manner that potentiates the activity of CPT-11 without producing significant side effects because Wang et al. and Chen et al. have taught an mdm-2 oncogene as a novel target for human cancer therapy using an oligonucleotide approach. One of ordinary skill in the art would have been motivated to modify the phosphorothioate oligonucleotide to include oligonucleotide phosphorothioate oligonucleotides with 2'-O-methylribonucleoside modifications at varying positions and had a reasonable expectation of success since the art taught the use of modified phosphorothioate oligonucleotides as particularly useful therapeutics for oral administration (Baracchini et al.).

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-8724 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
June 17, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635